

SILYLATION OF 6-PYRIDAZONE DERIVATIVES

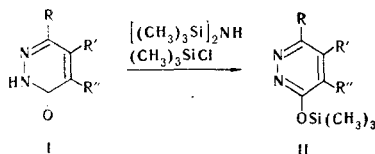
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Reaction of 6-pyridazone derivatives with hexamethyldisilazan in the presence of small amounts of trimethylchlorosilane gave trimethylsiloxy, bis(trimethylsiloxy), trimethylsiloxy (trimethylsilylamino), and N-trimethylsilylacetamido derivatives of pyridazine, the structures of which as O-trimethylsilyl compounds were confirmed by investigation of their UV, IR, and PMR spectra.

We have previously synthesized analogs of nucleosides of 3-hydroxy-6-pyridazone by means of trimethylsilyl derivatives of pyridazine [1]. The present paper is devoted to the silylation of 3-, 4-, and 5-substituted 6-pyridazones (Ia-k) and to a study of the structure of the compounds obtained. Up until our investigation, the literature contained only individual data on the silylation of pyridazinone Ic [2, 3].

The silylation of Ia-k was carried out with excess hexamethyldisilazan (HMDS) with a small amount (10:1) of trimethylchlorosilane (TCS) [4]. The yields of II were 60-80% (Table 3).



It is interesting to note that 4-amino derivatives II, j are silylated with appreciably greater difficulty than 3-amino derivative Id. This decrease in the reactivity of the exocyclic nitrogen atom with respect to nucleophilic substitution at silicon in HMDS for the amino group in the 4 position (II, j) as compared with the amino group attached to C₃ (Id) is due to the difference in the conjugation of the amino groups with the ring and, possibly, the effect of the halogen atom in the 5 position. It is known that the carbon atom in the 4 position of the pyridazone ring has the highest specific positive charge. In this connection, the multiplicity of the C-N bond increases, whereas S character is displayed to a great degree in the case of the N-H bond, and this should lead to an increase in the frequency of the stretching vibration of the latter. In fact, absorption bands at 3285 and 3390 cm⁻¹, which are shifted to 3330 and 3410 cm⁻¹ in the case of pyridazinones II, j, are observed in the spectrum of Id.

The starting bases, being cyclic amides, are capable of lactam-lactim tautomerism [5, 6], in connection with which the formation of O- (O,O-), N- (N,N-), or O,N-trimethylsilyl derivatives is possible during their silylation. The choice among these structures can be made on the basis of the UV, IR, and PMR spectra of the compounds.

The structures of 3-methoxy- (IIa), 3-chloro- (IIb), and 4,5-dihalo-6-trimethylsiloxy-pyridazines (IIg, h), and 3,6-bis(trimethylsiloxy)pyridazine (IIc) and its 4,5-dihalo derivatives (IIe, f) were confirmed by the presence in their UV spectra of absorption maxima that are analogous to those in the spectra of the corresponding O- or O,O-methyl derivatives (Table 1). The spectra do not contain the absorption char-

* Deceased.

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TABLE 1. UV Spectroscopic Data*

Com- pound	R	R'	R''	R'''	N ₁ (6-pyri- dazone)	λ_{max} , nm
IIa	OCH ₃	H	H	OSi(CH ₃) ₃	—	288
IIc	OSi(CH ₃) ₃	H	H	OSi(CH ₃) ₃	—	289
III	OCH ₃	H	H	OCH ₃	—	288
IV	OCH ₃	H	H	—	CH ₃	316
Ia	OCH ₃	H	H	—	H	313
Ic	OH	H	H	—	H	319
IIb	Cl	H	H	OSi(CH ₃) ₃	—	282
V	Cl	H	H	OCH ₃	—	278
VI†	Cl	H	H	—	CH ₃	303
Ib	Cl	H	H	—	H	305
II d	NHSi(CH ₃) ₃	H	H	OSi(CH ₃) ₃	—	319
Id	NH ₂	H	H	—	H	343
VII	NH ₂	H	H	OCH ₃	—	310
VIII	Cl	H	H	Cl	—	276, 304 sh
II l	NHSi(CH ₃) ₃	H	H	Cl	—	313
IX	NH ₂	H	H	Cl	—	315
II e	OSi(CH ₃) ₃	Cl	Cl	OSi(CH ₃) ₃	—	297
X	OCH ₃	Cl	Cl	OCH ₃	—	296
XI†	OCH ₃	Cl	Cl	—	CH ₃	324
Ie	OH	Cl	Cl	—	H	323
II f	OSi(CH ₃) ₃	Br	Br	OSi(CH ₃) ₃	—	300
XII†	OCH ₃	Br	Br	OCH ₃	—	301
XIII f	OCH ₃	Br	Br	—	CH ₃	325
Ig	OH	Br	Br	—	H	324
II h	H	Cl	Cl	OSi(CH ₃) ₃	—	275, 280, 306 sh
XIV	H	Cl	Cl	OCH ₃	—	276
XV	H	Cl	Cl	—	CH ₃	300, 306, 315 sh, 330
Ig	H	Cl	Cl	—	H	297 sh, 304, 313
II h	H	Br	Br	OSi(CH ₃) ₃	—	279, 285, 310 sh
XVI	H	Br	Br	OCH ₃	—	281
XVII	H	Br	Br	—	CH ₃	303, 309, 318 sh, 332
Ih	H	Br	Br	—	H	303 sh, 308, 315, 330
II i	H	NHSi(CH ₃) ₃	Cl	OSi(CH ₃) ₃	—	281
II j	H	NH ₂	Cl	—	H	299, 306
II j	H	NHSi(CH ₃) ₃	Br	OSi(CH ₃) ₃	—	282
Ij	H	NH ₂	Br	—	H	300, 306
II k	H	NSi(CH ₃) ₃ COCH ₃	Cl	OSi(CH ₃) ₃	—	270
I k	H	NHCOCH ₃	Cl	—	H	294, 306, 315 sh, 328

* Because of the sensitivity of IIa-l to hydrolysis, it was impossible to determine the ϵ values, and the values of the maxima were therefore used for comparison of the spectra.

† Data from [7]. The abbreviation "sh" denotes a shoulder. The values corresponding to the inflections are presented in italics.

TABLE 2. Parameters of the PMR Spectra

Com- pound	Solvent	Chemical shifts, τ , ppm									$J_{4,5}$, Hz
		OSiCH ₃	NSiCH ₃	OCH ₃	COCH ₃	3H	4H	5H	NH, OH	NH ₂	
II a	C ₆ H ₁₂	9.66	—	6.08	—	—	3.33	3.33	—	—	—
Ia	Acetone	—	—	6.22	—	—	2.96	3.18	-1.42	—	9.9
IIc	C ₆ H ₁₂	9.66	—	—	—	—	3.39	3.39	—	—	—
Ic*	DMSO	—	—	—	—	—	2.99	2.99	-1.51	—	—
IIb	CCl ₄	9.58	—	—	—	—	2.68	3.16	—	—	9.0
Ib	Acetone	—	—	—	—	—	2.55	3.03	—	—	9.9
V†	CDCl ₃	—	—	5.89	—	—	2.62	3.04	—	—	9.1
II g	CCl ₄	9.51	—	—	—	1.21	—	—	—	—	—
Ig	DMSO	—	—	—	—	1.90	—	—	-3.65	—	—
II h	DMSO	9.53	—	—	—	1.30	—	—	—	—	—
Ih	DMSO	—	—	—	—	1.92	—	—	-2.55	—	—
II e	C ₆ H ₁₂	9.61	—	—	—	—	—	—	—	—	—
Ie	DMSO	—	—	—	—	—	—	—	-2.30	—	—
II f	C ₆ H ₁₂	9.61	—	—	—	—	—	—	—	—	—
If	DMSO	—	—	—	—	—	—	—	-2.25	—	—
II l	DMSO	—	9.69	—	—	—	2.56	2.96	3.42	—	9.6
IX	DMSO	—	—	—	—	—	2.64	3.12	—	3.38	8.4
Ii	DMSO	—	—	—	—	2.44	—	—	-2.40	3.28	—
II j	DMSO	9.54	—	—	—	1.51	—	—	—	4.84	—
Ij	DMSO	—	—	—	—	2.53	—	—	-2.35	3.31	—
II k	CCl ₄	9.55	9.66	—	8.11	1.81	—	—	—	—	—
I k	DMSO	—	—	—	7.80	1.50	—	—	—	—	—

* Data from [11].

† Data from [12, 13].

acteristic for the N- or O,N-methyl derivative and the starting bases. The N,N-trimethylsilyl structure is unlikely in the case of IIc, e, f because of the lower (than in the case of Si-O) strength of the Si-N bond and the considerable steric hindrance between adjacent $(\text{CH}_3)_3\text{Si}$ groups. In conformity with this, the absorption maximum at 336 nm characteristic for the N,N-methyl derivative [7] is not observed in their UV spectra.

3,6-Dimethoxy-4,5-dihalo- and 4,5-dihalo-6-methoxypyridazines (X, XII, XIV, and XVI) have not been previously described. However, the adsorption maxima that we calculated for them with the aid of increment values [7] are in agreement with the values obtained for IIe-h.

As seen from the data in Table 1, replacement of the chlorine atom in the 3 position of V and VIII by an amino group (to give VII and IX) causes a bathochromic shift of ~ 30 nm, but the absorption maximum in this case does not coincide with the maximum for pyridazinone Id (343 nm). A similar shift is observed in the spectra of 3-trimethylsilylamino-6-trimethylsiloxy pyridazine (IIId) and 3-trimethylsilylamino-6-chloropyridazine (IIl), which contain an $(\text{CH}_3)_3\text{SiNH}$ group, and this confirms their structure.

The close values of the absorption maxima of the 4-trimethylsilylamino-5-halo-6-trimethylsiloxy pyridazines (III, j) and IIg, h and the appreciable difference from the absorption maxima of pyridazinones II, j constitute evidence in favor of their structures.

The absorption band of the C=O group of a 6-pyridazone ($1650\text{--}1680\text{ cm}^{-1}$) is absent in the IR spectra of IIa-f, h-j and 4-N-trimethylsilylacetamido-5-chloro-6-trimethylsiloxy pyridazine (IIk). The spectra of IIb-f, h-k contain a band at $1080\text{--}1115\text{ cm}^{-1}$, which is due to vibrations of the Si-O-C structural group [8]; this band is weak in the case of IId-f, h but is intense in the case of IIb, c, i-k. The determination of these vibrations in the spectrum of IIa is hindered by the fact that they may overlap with the vibrations from the C-O-C structural group observed in the spectra of III [5], V, and VII in the same region.

The silylation of the amino group of IIId, i, j is proved by the fact that the absorption bands of an NH_2 are absent in the spectra of these compounds, and there is a very intense absorption band of a secondary amino group at 3325 , 3375 , and 3370 cm^{-1} , respectively. This band is found at 3275 cm^{-1} in the spectrum of IIl. The increase in the frequency in the spectra of III, j is apparently due to the greater conjugation in them of the $(\text{CH}_3)_3\text{SiNH}$ group with the ring as compared with IIId. This band is absent in the spectrum of IIk, and a very intense band corresponding to the carbonyl absorption of tertiary amides [8] is observed at 1665 cm^{-1} . On the basis of these data, it may be assumed that the $(\text{CH}_3)_3\text{Si}$ group is attached to an exocyclic nitrogen atom. In particular, the close (see [9]) shifts of the protons of the CH_3CO group in the PMR spectra of Ik and IIk (Table 2) constitute evidence in favor of this.

An intense absorption band at 768 cm^{-1} , which is related to the stretching vibrations of the Si- CH_3 group [8], is present in the IR spectra of IIa-f, h-k; it is found at 747 cm^{-1} only in the case of IIl. Compounds Ia-c [5], Id-f, h-k, III [5], IV, and VII-IX do not absorb in this region. A second very intense band, which is due to these same vibrations [8], is observed at 857 cm^{-1} in the spectra of IIe, f, h-k. In the case of IIa-d, l it may overlap with the band from the out-of-plane deformation vibrations of two adjacent ring C-H bonds in these compounds [10], which hinders its identification. The spectra of all of the investigated organosilicon derivatives of pyridazine contain a very intense absorption band at 1255 cm^{-1} , which is related to the deformation vibrations of the Si- CH_3 groups [8]. This band is absent in the spectra of pyridazinones Ia-c [5], Id-f, h-k, III [5], V, and VII-IX.

The O-trimethylsilyl structure of IIa-k is also confirmed by the PMR spectra (Table 2). The structure of IIa is confirmed by the characteristic (for the pyridazine structure) decrease in the shielding of the protons of the methoxy group in its spectrum as compared with the spectrum of Ia. In addition, in the spectrum of IIa one's attention is drawn to the equivalence of the protons of the heteroring, which is impossible for N_1 -substituted 6-pyridazones [11]. In the spectrum of IIc, the chemical shifts of the methyl protons, like the chemical shifts of the protons of the heteroring, are close to the corresponding values for IIa. Replacement of a methoxy group or an $(\text{CH}_3)_3\text{SiO}$ group in the 3 position by a chlorine atom (V, IIb) leads to an appreciable decrease in the constants of shielding of the ring protons and the $(\text{CH}_3)_3\text{SiO}$ group as compared with the spectra of IIa, c. The chemical shift of the methyl protons is even smaller in the spectra of IIg, h. However, the introduction of yet another $(\text{CH}_3)_3\text{SiO}$ group in the 3 position (IIe, f) increases the shielding of these protons. The chemical shifts of the protons of the $(\text{CH}_3)_3\text{SiO}$ group in the spectra of IIj, k are quite close to the values observed for IIg, h.

It has been shown [12] that the chemical shifts of the ring protons in substituted pyridazines can be calculated via an additive scheme that takes into account the effect of the nature and position of the sub-

TABLE 3. Characteristics of the Compounds

Com- pound	bp (mm), °C	mp, °C	Empirical formula	Found, %					Calc., %					Yield, %
				C	H	Br	Cl	Si	C	H	Br	Cl	Si	
IIa	82-83 (2)	54-56	C ₈ H ₁₄ N ₂ O ₂ Si	48,6	7,2	—	—	14,5	48,4	7,1	—	—	14,2	66
IIb	85-87 (1)	74-76	C ₇ H ₁₁ ClN ₂ O ₂ Si	41,6	5,4	—	17,7	14,0	41,5	5,5	—	17,5	13,8	82
IIc	88-90 (2)	60-62	C ₁₀ H ₂₀ N ₂ O ₂ Si ₂	46,9	7,9	—	—	21,3	46,8	7,9	—	—	21,9	78
IId	210 (2) [†]	123-125*	C ₁₀ H ₂₂ N ₂ O ₂ Si ₂	47,3	8,6	—	—	22,0	47,0	8,3	—	—	22,0	69
IIe	112-113 (3)	55-56	C ₁₀ H ₁₈ Cl ₂ N ₂ O ₂ Si ₂	36,8	5,6	—	21,8	17,5	36,9	5,6	—	21,8	17,3	82
IIf	125-127 (2)	71-72	C ₁₀ H ₁₈ Br ₂ N ₂ O ₂ Si ₂	28,9	4,4	38,5	—	13,4	29,0	4,4	38,6	—	13,6	73
IIg	81-82 (2)	—	C ₇ H ₁₀ Cl ₂ N ₂ O ₂ Si	35,6	—	—	—	11,4	35,4	—	—	—	11,8	80
IIh	112-113 (2)	48-50*	C ₇ H ₁₀ Br ₂ N ₂ O ₂ Si	26,0	3,4	49,0	—	8,7	25,8	3,1	49,0	—	8,6	83
IIi	133-135 (1)	120-123*	C ₁₀ H ₂₀ ClN ₃ O ₂ Si ₂	41,6	7,2	—	12,2	19,2	41,4	6,9	—	12,2	19,4	46
IIj	132-133 (1)	84-86*	C ₁₀ H ₂₀ BrN ₃ O ₂ Si ₂	36,1	6,1	—	—	16,5	35,9	6,0	—	—	16,8	55
IIk	128-130 (2)	83-85*	C ₁₂ H ₂₂ ClN ₃ O ₂ Si ₂	43,7	6,8	—	10,5	16,9	43,4	6,7	—	10,7	16,9	63
IIl	143-144 (1)	127-130*	C ₇ H ₁₂ ClN ₃ Si	41,7	6,2	—	17,2	13,7	41,7	6,0	—	17,6	13,5	80

* The starting bases were obtained as a result of melting these compounds.

[†]Sublimes.

stituents on the resonance of the protons in the 4 and 5 positions. Using this approach, we calculated that the introduction of an $(\text{CH}_3)_3\text{SiO}$ group in the 3 position should cause an increase in the chemical shift of its protons by, on the average, 0.72 (4-H), 0.31 (5-H), and 0.41 (6-H) ppm. This is somewhat greater than the effect of a methoxy group (0.52, 0.14, and 0.36 ppm [12]). In addition, judging from the spectrum of III, the shielding effect of the $(\text{CH}_3)_3\text{SiNH}$ group in the same position on 4-H and 5-H is somewhat lower (0.51 and 0.15 ppm) than that of the amino group (0.67 and 0.23 ppm with respect to the spectrum of IX). This is probably due to the appreciable weakening of the p, π interaction with the heteroring at the exocyclic nitrogen atom in II because of the $p_\pi-d_\pi$ bonding of its unshared electron pair with the 3d orbitals of the silicon atom attached to it.

It may be assumed that the $p_\pi-d_\pi$ bonding between the silicon and oxygen atoms in the O-trimethylsilyl derivatives does not affect the p, π conjugation of the latter with the π system of the heteroring, inasmuch as different unshared pairs of electrons of the oxygen atom participate in each of these types of interaction.

It should be noted that O-trimethylsilyl derivatives IIa-k have the greatest heteroaromatic character, and this is apparently the determining factor in the silylation of the substituted 6-pyridazones (Ia-k), as is observed for phthalazine derivatives [3].

EXPERIMENTAL

The IR spectra of hexachlorobutadiene (2000-4000 and 1300-1500 cm^{-1}) and Nujol (700-1800 cm^{-1}) suspensions of the compounds were obtained with a UR-20 spectrometer with NaCl and LiCl prisms. The UV spectra of dry dioxane solutions of the compounds were recorded with a UV-2 automatic recording spectrophotometer designed and constructed in the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR. The PMR spectra of 0.2-0.5 M solutions of the compounds in purified and dried acetone, carbon tetrachloride, dimethyl sulfoxide (DMSO), or cyclohexane were obtained with a Perkin-Elmer R-12A spectrometer (60 MHz) with cyclohexane as the internal standard.

3-Methoxy-6-trimethylsiloxypyridazine (IIa). A mixture of 6.3 g (0.05 mole) of Ia, 50 ml of HMDS, and 5 ml of TCS (the base to HMDS to TCS molar ratio was 1:2.4:0.39) was stirred and heated at 150-170° [17] (bath temperature) with complete protection from air moisture until Ia dissolved and ammonium chloride evolution ceased (4 h). The excess HMDS was removed by distillation at reduced pressure in a stream of dry nitrogen at a bath temperature no higher than 80°, and residue was vacuum-distilled.

Compounds IIb-h, k, l were similarly obtained, but the mixture was heated for 2 h in the case of IIf, h, and for 12 h in the case of IIk. The base-HMDS-TCS molar ratio was 1:5.7:0.93 for the preparation of III and 1:3.4:0.56 for IIj; the reaction time was 12 h. The yields and physical constants of the compounds obtained are presented in Table 3.

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